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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|----------------------|------------------|
| 09/845,153 | 05/01/2001 | Wei-Chiang Shen | 1696.0020008/RWE/BEC | 4085 |
| 26111 | 7590 | 03/30/2005 | EXAMINER | |
| STERNE, KESSLER, GOLDSTEIN & FOX PLLC 1100 NEW YORK AVENUE, N.W. WASHINGTON, DC 20005 | | | DESAI, ANAND U | |
| | | ART UNIT | PAPER NUMBER | |
| | | 1653 | | |

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 09/845,153 | SHEN ET AL. | |
| | Examiner | Art Unit | |
| | Anand U. Desai, Ph.D. | 1653 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 20 December 2004.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-11 and 16-19 is/are pending in the application.
 4a) Of the above claim(s) 1-8, and 16-19 is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 9-11 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
 Paper No(s)/Mail Date
- 4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____.
 5) Notice of Informal Patent Application (PTO-152)
 6) Other: _____

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group III, claims 9-11, drawn to a method for prolonging blood and tissue retention of a sulphydryl-containing compound, in the reply filed on December 20, 2004 is acknowledged. The traversal is on the ground(s) that there would be no serious burden on the Examiner to examine the claims of Groups II and III together as the methods are very closely related. This is not found persuasive because the methods are unrelated. As discussed in the requirement for restriction the inventions of groups II and III have different effects. It would be burdensome to search the combination of inventions II and III together.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-8, and 16-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on December 20, 2004. This application contains claims 1-8, and 16-19 drawn to an invention nonelected with traverse in Paper filed December 20, 2004. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 12-15, and 20-22 have been cancelled. Claims 9-11 are currently pending and are under examination.

Priority

3. Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 120. The priority date is January 25, 1995.

Information Disclosure Statement

4. The information disclosure statements (IDSs) submitted on June 14, 2004, September 26, 2003, and August 23, 2001 are being considered by the examiner.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 9-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. In claim 9, it is not definite what is encompassed by the phrase, "lipid-containing moiety?" In claim 10, and 11, it is not definite what is encompassed by the word, "lipid?"

Lipids include many types of compounds containing a wide variety of functional groups. Chemists have divided this large family of compounds into two major classes: the complex lipids and the simple lipids. Complex lipids are those that are easily hydrolyzed to simpler constituents. Most complex lipids are esters of long-chain carboxylic acids called fatty acids. The simple lipids are those that are not easily hydrolyzed by aqueous acid or base. This term often seems inappropriate, because many of the so-called "simple" lipids are quite complex molecules. Three important groups of simple lipids are steroids, prostaglandins, and the terpenes (Wade, L. G. Organic Chemistry (1987), Chapter 27, page 1264).

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 9-11 are rejected under 35 U.S.C. 102(a) as being anticipated by Ekrami, H. dissertation (April 1994). Ekrami's dissertation is a document by another, because only Ekrami is the author of the dissertation. The current application priority date is January 25, 1995, and the Ekrami dissertation is dated April 1994 (see cover sheet). Ekrami, H. discloses the synthesis of Bowman-Birk Protease Inhibitor conjugated to palmitic acid via a reducible disulfide bond. The resulting compound would anticipates formula VI, wherein R¹ is -H, R³ is -OH, and R² is a lipid-containing moiety (see page 130, figure 1, abbreviated as BBIssPal throughout dissertation). Ekrami, H. shows the prolonged retention of ¹²⁵I-BBIssPal in the stomach, intestines, and colon of CF-1 mice to a greater extent than ¹²⁵I-Bowman-Birk Protease Inhibitor (see page 196, section 15, and page 197, figure 37, current application, claims 9-11).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller, C. et al. (International Journal of Pharmaceutics 57: 41-47 (1989)) in view of Chekhonin, V. et al. (FEBS Letters 287: 149-152 (1991)) and Fix, J. et al. (Am. J. Physiol. 251: G332-G340 (1986)).

Muller, C. et al. disclose the synthesis and disulfide bond cleavage of lipophilic disulfide prodrugs. Muller, C. et al. couple 6-mercaptopurine thiol derivatives to lipophilic compounds via disulfide bonds to prepare lipophilic prodrugs (6-MP prodrug) (see Materials and Methods, particularly Compound 2: 6-(octadecyldithio)purine, and Compound 10: 6-[2,3-bis-(octadecanoyloxy)propyl-1-dithio]purine). The 6-MP prodrug, compound 2 was used in a lymphocyte proliferation assay to demonstrate the disulfide bond cleavage is a cell-dependent

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process (see Results section, Disulfide cleavage). Muller, C. et al. does not describe the covalently coupling of long alkyl chains to proteins.

Chekhonin, V. et al. discloses the direct coupling of fatty acid acylation of Fab-fragment peptides (see Materials and Methods, page 150, section 2.3 Modification of antibody Fab-fragments). Fix, J. et al. disclose the increase in the plasma concentration of a somatostatin peptide analog with a palmitoylcarnitine fatty acid (see Figure 2, page G335, black circle). One would have been motivated to conjugate a protein, such as the peptide fragment disclosed by Chekhonin, V. et al. with a lipophilic compound using a disulfide bond as disclosed by Muller, C. et al. to increase the concentration of a protein pharmaceutical in a site specific manner as suggested by both Fix, J. et al. and Chekhonin, V. et al. Therefore it would have been obvious to the person having ordinary skill in the art to form a peptide-lipid sulfhydryl-containing compound to prolong blood and tissue retention of the peptide-lipid sulfhydryl-containing compound (current application, claims 9-11).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 9:00 a.m. - 5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (517) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 16, 2005



KAREN COCHRANE CARLSON, PH.D.
PRIMARY EXAMINER